Diurnal Variation in Fasting Plasma Glucose

Implications for Diagnosis of Diabetes in Patients Examined in the Afternoon

Rebecca J. Troisi, ScD
Catherine C. Cowie, PhD
Maureen I. Harris, PhD, MPH

Context Current diagnostic criteria for diabetes are based on plasma glucose levels in blood samples obtained in the morning after an overnight fast, with a value of 7.0 mmol/L (126 mg/dL) or more indicating diabetes. However, many patients are seen by their physicians in the afternoon. Because plasma glucose levels are higher in the morning, it is unclear whether these diagnostic criteria can be applied to patients who are tested for diabetes in the afternoon.

Objectives To document diurnal variation in fasting plasma glucose levels in adults not known to have diabetes, and to examine the applicability to afternoon-examined patients of the current diagnostic criteria for diabetes.

Design, Setting, and Participants Analysis of data from the US population–based Third National Health and Nutrition Examination Survey (1988-1994) on participants aged 20 years or older who had no previously diagnosed diabetes, who were randomly assigned to morning (n=6483) or afternoon (n=6399) examinations, and who fasted prior to blood sampling.

Main Outcome Measures Fasting plasma glucose levels in morning- vs afternoon-examined participants; diabetes diagnostic value for afternoon-examined participants.

Results The morning and afternoon groups did not differ in age, body mass index, waist-to-hip ratio, physical activity index, glycosylated hemoglobin level, and other factors. Mean (SD) fasting plasma glucose levels were higher in the morning group (5.41 [0.01] mmol/L [97.4 {0.3} mg/dL]) than in the afternoon group (5.12 [0.02] mmol/L [92.4 {0.4} mg/dL]; $P<.001$). Consequently, prevalence of afternoon-examined participants with fasting plasma glucose levels of 7.0 mmol/L (126 mg/dL) or greater was half that of participants examined in the morning. The diagnostic fasting plasma glucose value for afternoon-examined participants that resulted in the same prevalence of diabetes found in morning-examined participants was 6.33 mmol/L (114 mg/dL) or greater.

Conclusions Our results indicate that if current diabetes diagnostic criteria are applied to patients seen in the afternoon, approximately half of all cases of undiagnosed diabetes in these patients will be missed.

JAMA. 2000;284:3157-3159 www.jama.com

THE CURRENT RECOMMENDATIONS for diagnosis of diabetes emphasize measurement of fasting plasma glucose [1] and are based on studies of plasma glucose measured in the morning after an overnight fast of at least 8 hours. However, many patients are seen by their physicians in the afternoon in an uncertain state of fasting; moreover, plasma glucose has been observed to be higher in the morning.[2,3] Thus, it is unclear whether the current diagnostic criteria for diabetes can be applied to patients examined in the afternoon. We investigated this issue in a large, population-based survey of adults not known to have diabetes.

METHODS

The Third National Health and Nutrition Examination Survey (NHANES III) [4] was conducted between 1988 and 1994, and included a representative sample of the US population. Participants were interviewed for sociodemographic information, medical history, and lifestyle characteristics, then randomly assigned to either a morning or afternoon examination that included anthropometric measurements and phlebotomy. Those assigned to the morning examination were asked to not eat or drink anything other than water after 8:30 PM the day preceding the examination. Those examined in the early afternoon were asked to eat breakfast but to not eat or drink anything other than water after 7:30 AM the day of the examination. Those examined in the late afternoon were asked to eat lunch but to not eat or drink anything other than water after 11:30 AM.

The survey included 18825 subjects, aged 20 years or older. We excluded those who had a prior diagnosis of diabetes or were pregnant (n=1827), did not have plasma glucose measured (n=2288), or who at-

Author Affiliations: Social and Scientific Systems Inc, Bethesda, Md (Dr Troisi); and the National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, Md (Drs Cowie and Harris).
Corresponding Author: Maureen I. Harris, PhD, MPH, National Institute of Diabetes and Digestive and Kidney Diseases, Room 695, 6707 Democracy Blvd, MSC-5460, Bethesda, MD 20892 (e-mail: mh63q@nih.gov).

tended an examination session other than that to which they were assigned (n=617), as well as morning subjects who fasted fewer than 8 hours and afternoon subjects who fasted fewer than 4 hours (n=1211). Median fasting time for those examined in the morning (n=6483) was 13.5 hours; 82% fasted 12 through 16 hours. Median fasting time for those examined in the afternoon (n=6399) was 7.0 hours; 76% fasted 4 through 10 hours.

Morning and afternoon blood samples were collected and processed identically. Whole blood was collected in vacuum tubes containing potassium oxalate and sodium fluoride and centrifuged immediately at 1500 *g* for 10 minutes. Plasma was frozen at −70°C until analysis. Plasma glucose was measured using a hexokinase reference method (Roche Diagnostics, Montclair, NJ). The coefficient of variation for this method was 1.6% at a glucose concentration of 5.5 mmol/L (100 mg/dL), and 1.8% for a glucose concentration of 27.8 mmol/L (500 mg/dL). Fasting plasma glucose levels were used to define undiagnosed diabetes (≥7.0 mmol/L [126 mg/dL]) and impaired fasting glucose (6.1-6.9 mmol/L [110-125 mg/dL]).[1]

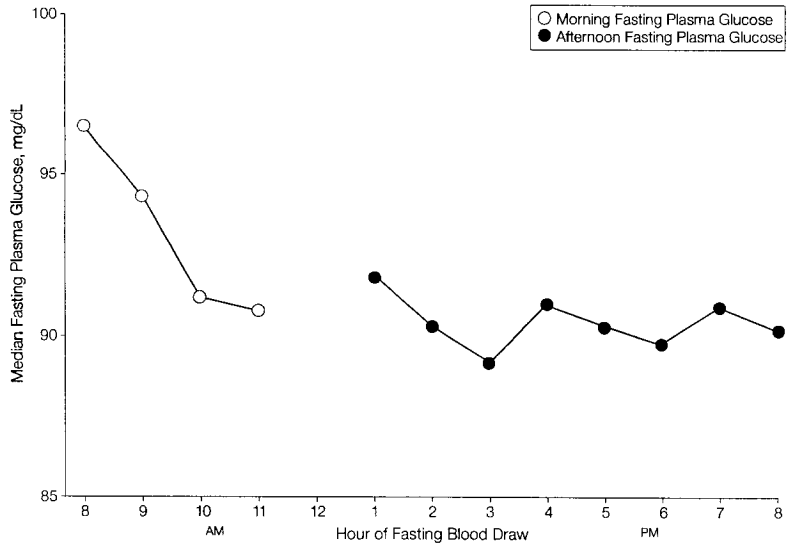
Statistical analyses were carried out using SAS (SAS Institute, Cary, NC) with survey sampling weights. Tests of statistical significance were calculated using SUDAAN (Research Triangle Institute, Research Triangle Park, NC). Means were compared using 2-tailed *t* tests. Trends were tested using linear regression with continuous values for the independent variables. Fasting glucose was log-transformed because of its skewed distribution. The protocol was reviewed and approved by the institutional review board of the National Center for Health Statistics, and informed consent was obtained from all participants.

Table. Characteristics of Subjects Examined in the Morning and Afternoon*

Characteristic	Morning (n = 6483)	Afternoon (n = 6399)	*P* Value
Age, mean, y	44.3 (0.5)	44.8 (0.6)	.33
Men, %	48.1 (0.8)	48.4 (0.8)	.83
Race, %			
White	77.1 (1.4)	78.0 (1.5)	.50
Black	10.0 (0.6)	9.7 (0.7)	.56
Mexican-American	5.0 (0.5)	4.9 (0.4)	.56
Other	7.9 (0.6)	7.4 (0.6)	.50
Parental history of diabetes, %	18.5 (0.9)	17.9 (0.6)	.51
Body mass index, mean, kg/m^2	26.4 (0.1)	26.5 (0.1)	.55
Waist-to-hip ratio, mean	0.90 (0.00)	0.91 (0.00)	.16
Physical activity index, mean	114.5 (4.2)	108.3 (3.3)	.17
Current cigarette smoker, %	30.6 (1.0)	31.3 (1.0)	.50
Current alcohol drinker, %	53.5 (1.7)	53.0 (1.8)	.78
Some college education or more, %	43.7 (1.3)	41.6 (1.5)	.12
Current oral contraceptive use, %†	15.8 (1.2)	17.4 (1.2)	.28
Current hormone replacement therapy use, %‡	18.8 (1.6)	21.2 (1.8)	.32
Other medication use, %§	16.1 (0.7)	15.6 (0.9)	.52
Glycosylated hemoglobin, mean, %	5.26 (0.02)	5.25 (0.02)	.60

*Data in parentheses are SEs.
†Women aged 20-49 years.
‡Women aged >40 years.
§Medications that may affect glucose levels include diuretics, calcium channel blockers, β-blockers, α-blockers, angiotensin-converting enzyme inhibitors, growth hormone, and corticosteroids.

Figure. Median Fasting Plasma Glucose by Hour of Blood Draw



To convert glucose values to mmol/L, multiply by 0.0555.

RESULTS

Subjects examined in the morning and afternoon were similar in age, sex, race, parental history of diabetes, body mass index, waist-to-hip ratio, physical activity, smoking status, alcohol intake, education, use of medications that may affect glucose levels, and glycosylated hemoglobin levels (TABLE).

Mean (SD) fasting plasma glucose levels were higher in the morning group (5.41 [0.01] mmol/L [97.4 [0.3] mg/dL]) than in the afternoon group (5.12 [0.02] mmol/L [92.4 [0.4] mg/dL]; $P<.001$). Fasting plasma glucose was highest in those examined in the early morning and declined throughout the morning (test for trend, $P<.001$) (FIGURE). Afternoon fasting glucose val-

ues were more stable and were similar to late-morning levels ($P=.57$). Length of fast (morning >8 hours; afternoon >4 hours) was not an important factor. In morning subjects, there was a nonsignificant increase in mean plasma glucose from 5.38 mmol/L (97.0 mg/dL) in those who fasted 8 through 12 hours to 5.40 mmol/L (97.3 mg/dL) in those who fasted 16 hours or more. In afternoon subjects, there was a clinically insignificant decrease from 5.13 mmol/L (92.5 mg/dL) in those who fasted 4 through 8 hours, to 5.06 mmol/L (91.2 mg/dL) in those who fasted 12 hours or more.

Fasting plasma glucose increased with age, but morning subjects had higher glucose values at every age compared with afternoon subjects, with an overall mean difference of 0.28 mmol/L (5.0 mg/dL) ($P<.001$). Consequently, prevalence in afternoon subjects of glucose values indicating diabetes (1.4%) was one half that of morning subjects (2.8%). Prevalence of glucose values indicating impaired fasting glucose in afternoon subjects (2.6%) was one third that of morning subjects (7.4%). There was no statistically significant trend by age in these disease prevalence ratios ($P>.50$), even though prevalence of both conditions increased markedly with increasing age. For example, among those aged 60 years or older, the prevalence of undiagnosed diabetes in morning subjects was 7.0%; in afternoon subjects, the prevalence of those with fasting plasma glucose levels of 7.0 mmol/L (126 mg/dL) or greater was only 3.5%.

Because the morning and afternoon groups were virtually identical except for fasting plasma glucose, it would be expected that diabetes prevalence would also be identical in the 2 groups. We used this feature to determine the glucose values that would be diagnostic for diabetes and impaired fasting glucose in afternoon subjects. Under the current diagnostic criteria, derived from subjects examined in the morning, the fasting plasma glucose value distinguishing diabetic from nondiabetic individuals is 7.0 mmol/L (126 mg/dL). In NHANES III, this corresponds to the 97.2th percentile of fasting plasma glucose (diabetes prevalence of 2.8%). For afternoon subjects, the 97.2th percentile value for fasting glucose was 6.33 mmol/L (114 mg/dL). Similarly, the diagnostic value for impaired fasting glucose (6.11 mmol/L [110 mg/dL]) in morning subjects corresponded to the 89.8th percentile; this value in afternoon subjects was 5.66 mmol/L (102 mg/dL).

As found for glucose, mean fasting serum insulin and C peptide levels were significantly higher in subjects examined in the morning (61.9 pmol/L and 0.696 nmol/L, respectively), compared with those examined in the afternoon (56.3 pmol/L and 0.635 nmol/L) ($P<.001$ for both analytes).

COMMENT

These data from a nationally representative sample of adults demonstrate that there are clinically significant differences in fasting plasma glucose levels between subjects examined in the morning and in the afternoon. We estimate that glucose values indicating diabetes for patients tested in the afternoon should be fully 0.67 mmol/L (12 mg/dL) lower than the current diagnostic criterion of 7.0 mmol/L (126 mg/dL) or greater. If the current criterion were applied to afternoon patients, about half the cases of undiagnosed diabetes would be missed in this group. Indeed, because of the consistent decline in fasting plasma glucose throughout the morning, even the difference between 8 AM and 10 AM glucose values can be significant.

Many patients in the ambulatory care setting are seen in the afternoon, and these patients can be asked to fast for at least 4 hours before testing for diabetes. Regardless of the time of day that patients are tested, physicians need to confirm the diagnosis by repeat testing on a different day. For those initially tested in the afternoon, a confirmatory morning test may be advised.

Early morning rises in fasting glucose levels and insulin requirements (the "dawn phenomenon") have been observed in patients with diabetes [2] and in some,[3,5,6] but not all,[7-9] studies of nondiabetic persons. Nocturnal elevations in growth hormone and early morning increases in cortisol secretion have been explored as contributors to this phenomenon.[10-13] Our data showing higher fasting levels of plasma glucose, serum insulin, and serum C peptide in morning subjects are consistent with the existence of a dawn phenomenon in nondiabetic subjects.

REFERENCES

1. Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care*. 1999;22:S5-S19.
2. Bolli GB, Gerich JE. The "dawn phenomenon": a common occurrence in both non-insulin-dependent and insulin-dependent diabetes mellitus. *N Engl J Med*. 1984;310:746-750.
3. Bolli GB, De Feo P, De Cosmo S, et al. Demonstration of a dawn phenomenon in normal human volunteers. *Diabetes*. 1984;33:1150-1153.
4. Harris MI, Flegal KM, Cowie CC, et al. Prevalence of diabetes, impaired fasting glucose, and impaired glucose tolerance in U.S. adults: The Third National Health and Nutrition Examination Survey, 1988-1994. *Diabetes Care*. 1998;21:518-524.
5. Schmidt MI, Lin QX, Gwynne JT, Jacobs S. Fasting early morning rise in peripheral insulin: evidence of the dawn phenomenon in nondiabetes. *Diabetes Care*. 1984;7:32-35.
6. Arslanian S, Ohki Y, Becker DJ, Drash AL. Demonstration of a dawn phenomenon in normal adolescents. *Horm Res*. 1990;34:27-32.
7. Simon C, Brandenberger G, Follenius M. Absence of the dawn phenomenon in normal subjects. *J Clin Endocrinol Metab*. 1988;67:203-205.
8. Mauras N, Rogol AD, Clarke WL. Failure to detect the "dawn phenomenon" in nondiabetic subjects with markedly different patterns of nocturnal growth hormone secretion. *J Clin Endocrinol Metab*. 1986;62:975-979.
9. Marin G, Rose SR, Kibarian M, Barnes K, Cassorla F. Absence of dawn phenomenon in normal children and adolescents. *Diabetes Care*. 1988;11:393-396.
10. Campbell PJ, Bolli GB, Cryer PE, Gerich JE. Pathogenesis of the dawn phenomenon in patients with insulin-dependent diabetes mellitus: accelerated glucose production and impaired glucose utilization due to nocturnal surges in growth hormone secretion. *N Engl J Med*. 1985;312:1473-1479.
11. Trumper BG, Reschke K, Molling J. Circadian variation of insulin requirement in insulin dependent diabetes mellitus: the relationship between circadian change in insulin demand and diurnal patterns of growth hormone, cortisol and glucagon during euglycemia. *Horm Metab Res*. 1995;27:141-147.
12. Scheen AJ, Van Cauter E. The roles of time of day and sleep quality in modulating glucose regulation: clinical implications. *Horm Res*. 1998;49:191-201.
13. Van Cauter E, Polonsky KS, Scheen AJ. Roles of circadian rhythmicity and sleep in human glucose regulation. *Endocrinol Rev*. 1997;18:716-738.